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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/888,326	Applicant(s) WEINER ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-22,24,34,43,56 and 76* is/are pending in the application.

4a) Of the above claim(s) *3,4,22 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-15,17-21,24,34,43 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 7/11/03, as Paper No. 18. The amendment has been entered. Claim 16 has been cancelled. Claims 1, 2, 5, 6, 12, 13, 15, 17-21, 24, 34, 43 and 56 have been amended. Claims 1-22, 24, 34, 43, 56 and 76 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Claims 3, 4, 22, and 76 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, for the reasons of record. Applicant timely traversed the restriction (election) requirement in Paper No. 12 (10/15/02).

4. Claims 1, 2, 5-15, 17-21, 24, 34, 43 and 56 are examined herein.

5. This application contains claims 3, 4, 22 and 76 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

Applicants indicated in the communication filed 7/11/03 that they did not receive an initialed/signed copy the IDS (PTO-1149) filed on 9/28/01 or 9/30/02. It is noted that although the IDS forms mentioned were received by the Office, the forms (PTO-1449s) and related references are not currently present in the Application's file, and thus appear to be lost. Applicants are asked to supply new copies of the IDS 1449s so that the Office can obtain copies of the appropriate references for consideration. Upon receipt of the appropriate IDS forms, the Examiner will obtain copies of the sited references and return an initialed/signed copy of the IDS forms.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 5-15, 17-21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for:

A method for inhibiting B-cell lymphoma tumor growth comprising administering to a subject having a B-cell lymphoma tumor:

a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and further comprises a phosphorothioate modified backbone, wherein said immunostimulatory CpG nucleic acid is administered in an amount effective to upregulate CD20 expression in said B-cell lymphoma; and

b) an anti-CD20 antibody;

wherein administration of the immunostimulatory CpG nucleic acid and anti-CD20 antibody results in the inhibition of B-cell lymphoma tumor growth;

does not reasonably provide enablement for all embodiments embraced by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the specification is not enabling for claims drawn to: **preventing** cancer in a subject, and immunostimulatory nucleic acids that are less than 6 nucleotides in length, nucleotides which do not contain an unmethylated CpG motif, and nucleotides which not contain a modified backbone.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention:

The instant claims are drawn to a method of treating or preventing cancer by administering: a) a nucleic acid in an amount effective to upregulate CD20 expression and b) and anti-CD20 antibody. Therefore the general nature of the invention is cancer therapy and encompasses a administrating a combination of an anti-CD20 antibody and a nucleic acid.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass treating or preventing any kind of cancer by administering any nucleic acid which upregulates CD20 expression (including a nucleic acid which encodes and expresses an CD20, as well as oligonucleotides which induce anti-CD20 expression) and an anti-CD20 antibody.

The unpredictability of the art and the state of the prior art:

It is noted that the claim encompasses administering any nucleic acid which upregulates CD20 expression, thus the claim embraces administering a nucleic acid encoding CD20 or a factor which induces expression of CD20. Therapeutic administration of a nucleic acid encoding and expressing a polypeptide is a method of gene therapy.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear" (see page 409, first col.), and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not recognized by the immune system, stable and easy to reproduce... Finally it would express the

gene (or genes) it requires for as long as long as required in an appropriately regulated fashion." (See p. 409, second column).

More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section). Walther and Stein also indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

Regarding the unpredictable nature of cancer gene therapy, Greco et al. (Front. Biosci. Vol. 7:d1516-24; 2002) teaches,

> "Some major problems remain to be solved before this strategy becomes routinely adopted in the clinic, one of the main challenges being the improvement of gene delivery. Namely, the development of DNA vectors characterized by maximum efficiency and minimal toxicity will define the success of gene therapy and its chances of being accepted by public and clinicians. A number of issues need to be considered. The "magic" vector should be targeted, protected from degradation and immune attack, and safe for the recipient and the environment. Moreover, it should express the therapeutic gene for as long as required, in an appropriately regulated fashion." (See p. d1516, abstract).

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs, 1998; 5:341-346) teaches,

> "Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity." (See p. 342, first paragraph).

Similarly, Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches, "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory

activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT" (See p. 115, first paragraph). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans.

Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (See p. 1618, first column).

Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

There is no teaching in the prior or post-filing art indicating that any cancer can be prevented, thus indicating the high degree of unpredictability of preventing cancer. In fact, methods for preventing cancer would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

Working Examples and Guidance in the Specification

The specification has one working example specifically indicating that when mice comprising a B-cell lymphoma (T3C cells), were administered CpG ODN 1826 (a 20mer oligonucleotide with a phosphorothioate backbone (SEQ ID NO: 560) and a mouse IgG2a monoclonal antibody (MS11G6), the mice had a significantly improved survival when compared to control mice (see Example 3, pages 76-77), thus indicating that the treatment inhibited growth of the B-cell lymphoma. The specification also provides guidance on constructing an immunostimulatory oligonucleotide comprising at least one umethylated CpG dinucleotide. The specification also indicates a general formula for the immunostimulatory oligonucleotide. It is disclosed that the CpG nucleic acid is represented by at least the formula (emphasis added):

5' $N_1X_1CGX_2N_2$ 3'

wherein X_1 and X_2 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic sequences composed of from about 0-25 N's each (see p. 38 of the specification).

It is noted that there are no examples or guidance indicating anything other than an immunostimulatory nucleic acid comprising an unmethylated CpG motif can be used to upregulate CD20 expression. Also, there are no examples or guidance disclosing the method as useful for treating any kind of cancer other than a B-cell lymphoma, and there is no example/guidance indicating that cancer was prevented.

Quantity of Experimentation

Considering the breadth of the claims and the limited working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims with a reasonable expectation of success. For instance, there is no indication in the specification or

prior art that a nucleic acid encoding an tumor antigen (such as CD20) could be effectively delivered to any cancer in vivo in such a way that resulted in the proper expression of the antigen and proper display of the antigen on the surface of the cancer cell at a concentration high enough, and for a long enough duration of time in order to effectively treatment or prevent any cancer. Considering the teaching in the art and the examples and guidance in the specification, one of skill in the art could use the method for inhibiting growth of a B-lymphoma tumor provided the nucleic acid comprises an oligonucleotide comprising at least one unmethylated CpG motif, at least 6 nucleotides in length, and has a phosphorothioate modified backbone. However, additional experimentation would be required in order to use any nucleic acid that does not specifically have these characteristics to treat or prevent any type of cancer. For instance, one would have to show how a nucleic acid comprising only methylated CpG motifs could function as immunostimulatory molecules, considering the teaching in the art that it is imperative to have at least one unmethylated CpG motif. Also, additional experimentation would have to be done in order to overcome the teaching in the art that the ODNs must be administered in a form that protects them from nuclease degradation and that the nucleic acid must be at least 6 nucleotides in length in order to be effective. The amount of additional experimentation is deemed to be undue because in order to practice the full scope of the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broad method would not work for treating or preventing any cancer.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability of recognized in the art, particularly the problems associate with gene therapy and the required characteristics of the nucleic acid in order to be an effective in vivo immunostimulatory nucleic acid sequence; 2) the breadth of the claims as mentioned above; 3) the limited number of working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Response to Arguments

8. Applicant's arguments filed 7/11/03 have been fully considered but they are not persuasive.

9. Applicants contend that the claims have been amended to such that the instant clams are drawn to administering an immunostimulatory nucleic acid that upregulates CD20 expression and an anti-CD20 antibody. Applicants argue that the specification provides a detailed description of the immunostimulatory nucleic acids. Applicants also contend that the issues related to preventing genetic mutation and immortaliztation are not relevant to the instant claims (see p 16 of the response filed 7/11/03). Applicants also assert that the specification teaches how to identify other immunostimulatory nucleic acids which can be used to stimulate CD20 expression; therefore it would not be undue experimentation to identify the other nucleic acids.

10. In response, it is respectfully pointed out that the claims still encompass administering any nucleic acid including oligonucleotides less than 6 nucleotides in length and including nucleotides without an unmethylated CpG motif and without a modified backbone. Considering

the prior art, as indicated in the previous Office Action (and reiterated above) teaches that the immunostimulatory nucleic acids **must be greater than 6 nucleotides in length, must contain an unmethylated CpG motif, and must have a modified backbone to protect it from degradation**, Applicants arguments are not persuasive.

Regarding the Applicants argument that preventing genetic mutation and immortalization are not relevant to the instant claims, it is respectfully pointed out that the claims are specifically drawn to methods of preventing cancer in a subject at risk of developing cancer. Furthermore, the specification indicates that the method can treat cancer by "preventing the growth of a cancer cell by decreasing or slowing the rate of growth, **by inhibiting growth altogether**, or by killing or inducing apoptosis of the cancer cell" (see p. 32, lines 3-5). Therefore, the claims are properly interpreted as encompassing completely preventing the occurrence of any future cancer growth in a subject by inhibiting cancer cell growth altogether—which includes inhibiting cancer growth due to genetic mutation and immortalization.

Regarding Applicants arguments that the specification teaches methods to identify other immunostimulatory nucleic acids that induce CD20 expression. It is acknowledged that the specification teaches how to identify such nucleic acids. However, there is no indication that the method has identified immunostimulatory nucleic acids that are functional in the claimed method and that are 1) less than 6 nucleotides in length, 2) without an unmethylated CpG motif, 3) without a modified backbone. Considering the prior art indicates that the immunostimulatory nucleic acids must be at least 6 nucleotides in length, have at least one unmethylated CpG motif, and have a modified backbone to prevent degradation, Applicants arguments are not persuasive.

Therefore, the rejection is appropriate and the rejection is not withdrawn.

11. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim is drawn to a method for treating or preventing cancer in a subject by administering to a subject an immunostimulatory nucleic acid in an amount effective to induce expression of CD19 or CD22 antigen on the surface of a cancer cell; and further administering an anti-CD19 or antio-CD22 antibody to said subject.

The instant claims encompass administering any immunostimulatory nucleic acid that induces CD19 or CD22 expression on the surface of a cancer cell. However, the specification has not specifically identified which immunostimulatory nucleic acids are capable of inducing CD19 or CD22 expression in cancer cells.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

In the instant case, the specification has identified a number of immunostimulatory nucleic acids (see p. 46-51 of the specification). The specification has also identified methods

for testing the ability of a nucleic acid to induce expression of specific antigens, such as CD20 (see Figures 1-5, and Examples 1-3); however, the specification has not explicitly identified any immunostimulatory nucleic acids which induce the expression of CD19 or CD22 on the surface of cancer cells. Therefore, the specification has not sufficiently described a representative number of species of immunostimulatory nucleic acids which induce the expression of CD19 and/or CD22 expression on the surface of cancer cells.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses administration of any immunostimulatory nucleic acid which induces the expression of CD19 or CD22 in any type of cancer cell. As mentioned in the written description rejection above, the claim encompasses nucleic acid molecules which are not sufficiently described in the specification. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a representative number of immunostimulatory nucleic acids which induce CD19 or CD22 expression in cancer cells would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21,

1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, although a number of immunostimulatory nucleic acids have been identified in the specification, the is no evidence presented that any of these immunostimulatory nucleic acids induce CD19 or CD22 expression in cancer cells. It is respectfully pointed out that Figures 1-5 appear to only indicate that certain immunostimulatory nucleic acids can induce CD20 expression in cancer cells. There does not appear to be any indication of the immunostimulatory molecules which induces CD19 or CD22 expression in cancer cells. Applicants are asked to indicate the specific page and line numbers which indicate the specific immunostimulatory nucleic acids which induce expression of CD19 and CD22 in cancer cells. Without a clear indication of the immunostimulatory nucleic acids which can induce CD19 and CD22 expression in cancer cells, one of skill in the art cannot practice the claimed method without performing an undue amount of additional experimentation. Furthermore, the claims encompass preventing cancer. As indicated above, the claims are properly interpreted as encompassing preventing the future occurrence of cancer in an individual not having cancer. Considering the prior art of record, which indicates that there are no methods to absolutely prevent the future occurrence of cancer, and further considering there are no examples which indicate that the claimed method can prevent cancer in an individual, it is concluded that the an undue amount of additional experimentation would have to be done in order to practice the claimed method to the full scope encompassed by the claim.

It is noted that if the immunostimulatory nucleic acids which induce CD19 and CD22 expression are the unmethylated CpG oligonucleotides similar to claims 1, 2, 5-15 and 17-21; that the claim must be limited to immunostimulatory nucleic acids least 6 nucleotides in length

comprising at least one unmethylated CpG motif and comprising a modified backbone to protect the nucleotide from degradation for the reasons set forth above in the rejection of claims 1, 2, 5-15, 17-21.

Response to Arguments

12. Applicant's arguments filed 7/11/03 have been fully considered but they are not persuasive.

Applicants argue that the claim has been amended to limit the claim to a method comprising administering an immunostimulatory nucleic acid which induces the expression of CD19 or CD22 in cancer cells. Applicants argue that the specification has described a large number of immunostimulatory nucleic acids, and have described methods to identify which nucleic acids induce CD19 and CD22 expression in cancer cells.

In response, it is acknowledged that the specification has identified a large number of "immunostimulatory nucleic acids"; however, the specification has only identified these molecules as molecules which induce the expression of CD20 (See figures 1-5). There is no indication that the disclosed immunostimulatory nucleic acids induce CD19 or CD22 expression in cancer cells. Without a clear indication of the immunostimulatory nucleic acids which induce CD19 or CD22 expression in cells one of ordinary skill in the art would be required to perform additional experimentation in order to identify which nucleic acids stimulate CD19 or CD22 expression in cancer cells. Therefore, the claims are appropriately rejected under 35 USC 112, first paragraph and the rejections are not withdrawn.

13. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

In the instant case the claim encompasses first identifying any surface antigen that is not on the surface of or is present at a lower level than in a B-cell lymphoma cell compared to a normal B-cell, and then administering an antibody specific for said antigen and a nucleic acid which upregulates the expression of said antigen on the surface of a the B-cell.

Therefore, the claims encompass molecules for which there is insufficient written description provided in the specification. Specifically, the claims encompass B-cell lymphoma specific antigens which have not been adequately described; as well as immunostimulatory nucleic acids which have not been identified which induce the expression of the antigens.

The specification has identified CD19, CD20 and CD22 as the only cancer antigens present in cancerous B-lymphomas but to a lesser extent in than in normal B-cells. The specification indicates one species of immunostimulatory nucleic acid, which comprises an unmethylated CpG motif, is known to induce the expression a specific B-cell lymphoma antigen (CD20). However, there is no disclosure in the specification or the art which indicates the other B-cell lymphoma cancer antigens which are not present or present to a lower extent in B-cell lymphoma cells than normal B-cells. Furthermore, the disclosed species of immunostimulatory nucleic acids have only been shown to stimulate expression of CD20 antigen in cancer cells. There is no evidence indicating which of the described immunostimulatory nucleic acids stimulate antigens other than CD20. In particular there is no indication that the immunostimulatory nucleic acids disclosed are be capable of inducing the expression of any unidentified antigens. It is impossible to predict which nucleic acid molecules would be effective at upregulating expression of any unknown cancer antigens in a malignant B-cell. Therefore, the claim encompass antigens and nucleic acid molecules which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

14. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses first identifying any surface antigen that is not on the surface of, or is present at a lower level than in a B-cell lymphoma cell compared to a normal B-cell, then

treating the B-cell lymphoma by administering an antibody specific for said antigen and a nucleic acid which upregulates the expression of said antigen on the surface of a B-cell cancer cell. As mentioned in the written description rejection above, the claim encompasses antigens and immunostimulatory nucleic acid molecules that are not sufficiently described in the specification. Furthermore, there is no description of the antigens or the nucleic acid molecules that would induce the expression of the cancer antigens (other than CD20) in a B-cell lymphoma. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

Response to Arguments

15. Applicant's arguments filed 7/11/03 have been fully considered but they are not persuasive.

Applicants contend that the specification does not have to describe every possible B-cell cancer antigen. Applicants contend that the common features of the antigens are disclosed as a "surface antigen" which "is not expressed" or "is expressed on the surface of a B-cell in an amount lower than that of a normal B-cell" and the expression of each antigen can be upregulated by administering an "immunostimulatory nucleic acid". Applicants also contend that a detailed description of useful immunostimulatory nucleic acids is provided.

In response, it is acknowledged that the Applicants do not have to disclose every possible B-cell cancer antigen or every immunostimulatory nucleic acid which stimulates expression of the antigens. However, the specification has not adequately described the B-cell cancer antigens

encompassed by the claims. The Applicants have indicated how to identify possible B-cell cancer antigens: those which are not present or in expressed less in the B-cell lymphoma cells compared to normal cells. However, this is not a sufficient description of the structure of the antigens encompassed by the claim. In fact, it is an invitation to perform additional experimentation in order to identify the structure of the antigens. Furthermore, the disclosure that the common structures are "cell surface antigens" does not particularly describe in common structures of the antigens which would distinguish them from other non-cancerous cell surface antigens. Furthermore, without an adequate description of the cancer antigens encompassed by the claims, there is certainly not an adequate description of immunostimulatory nucleic acids which could induce their expression in cancer cells. Although the specification has described a large number of immunostimulatory nucleic acids, there is no indication that these nuclei acids can stimulate the expression of any cancer antigen other than CD20. There is certainly no indication that any of the described nucleic acids can stimulate an adequate number of B-cell cancer antigens encompassed by the instant claim, which have not yet been identified. Considering that in order to practice the claimed invention one of skill in the art would have to 1) identify an adequate number of the B-cell cancer antigens encompassed by the claims and then 2) identify the immunostimulatory nucleic acids which induce expression of these B-cell cancer antigens in cancer cells; it is concluded that an undue amount of experimentation would be required in order for one of skill in the art to be able to practice the claimed invention.

16. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

In the instant case the claim encompasses treating a lymphoma that is resistant to antibody therapy by administering an antibody specific for a surface antigen on said lymphoma and an immunostimulatory nucleic acid which upregulates the expression of said surface antigen on said lymphoma cell surface.

Therefore, the claims encompass molecules which are not adequately described in the specification. Specifically the claims encompass surface antigens which are not adequately described in the specification; and the claims encompass immunostimulatory nucleic acids which stimulate the expression of the surface antigens which have not been adequately described.

The specification indicates one species of immunostimulatory nucleic acid comprising an unmethylated CpG motif which is known to induce the expression of a certain cancer antigen (CD20) in lymphoma cells. However, there is no disclosure in the specification or in the art

which indicates that the disclosed species of immunostimulatory nucleic acids would upregulate expression of an adequate number of surface antigens encompassed by the claims. In particular, there is no indication that the described species would be capable of upregulating the expression of any unidentified antigens. It is impossible to predict which nucleic acid molecules would be effective at upregulating expression of any unknown antigens in a lymphoma cell resistant to antibody therapy. Therefore, the claim encompass antigens and nucleic acid molecules which are not adequately described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses treating a lymphoma that is resistant to antibody therapy by administering an antibody specific for a surface antigen on said lymphoma and an immunostimulatory nucleic acid which upregulates the expression of said surface antigen on said lymphoma cell surface. As mentioned in the written description rejection above, the claim encompasses surface antigens and immunostimulatory nucleic acid molecules which are not adequately described in the specification. Furthermore the description of the surface antigens and the immunostimulatory nucleic acid molecules which would induce the expression of the surface antigens provided is insufficient to adequately describe the entire genus of surface antigens and immunostimulatory nucleic acids encompassed by the claims. Therefore, additional

experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success.

In order to make and use the claimed invention, a representative number of surface antigens and a representative number of immunostimulatory nucleic acid molecules which stimulate expression of a sufficient number of surface antigens would have to be identified. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description).

In the instant case, no attributes or structural features common to the genus of surface antigens are disclosed. Identification of the necessary attributes/features common to all surface antigens and immunostimulatory nucleic acids encompassed by the claim is required. In order to practice the claimed method, additional experimentation is required to be able to identify the surface antigens encompassed by the claims and to be able to identify the immunostimulatory nucleic acids which induce the expression of the surface antigens. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

Response to Arguments

18. Applicant's arguments filed 7/11/03 have been fully considered but they are not persuasive.

Applicants argue that the claim does not require that a single nucleic acid upregulate the expression of every surface antigen. Applicants contend that the specification provides the common features of the antigens and immunostimulatory nucleic acids (similar to claim 34, above).

In response, it is acknowledged that the claim does not require that a single nucleic acid upregulate the expression of every surface antigen. However, the claims do encompass surface antigens and immunostimulatory nucleic acids which have not been adequately described in the specification. As mentioned above, the claims encompass surface antigens that include antigens that have not yet been identified. The specification only discloses the common feature of the antigens as a "surface antigen" which "is not expressed" or "is expressed on the surface of a B-cell in an amount lower than that of a normal B-cell" and the expression of each antigen can be upregulated by administering an "immunostimulatory nucleic acid". The disclosure that the common structures of the antigens as "cell surface antigens" does not particularly describe common structures of the antigens which would distinguish them from other non-cancerous cell surface antigens. Furthermore, without an adequate description of the cancer antigens encompassed by the claims, there is certainly not an adequate description of immunostimulatory nucleic acids which could induce their expression in cancer cells.

Although the specification has described a large number of immunostimulatory nucleic acids, there is no indication that these nucleic acids can stimulate the expression of any cancer antigen other than CD20. There is certainly no indication that any of the described nucleic acids can stimulate an adequate number of surface antigens encompassed by the instant claim, including those which have not yet been identified. Considering that in order to practice the

claimed invention one of skill in the art would have to 1) identify an adequate number of the surface antigens encompassed by the claims and then 2) identify the immunostimulatory nucleic acids which induce expression of these surface antigens in cancer cells; it is concluded that an undue amount of experimentation would be required in order for one of skill in the art to be able to practice the claimed invention.

19. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description guidelines are mentioned above.

In the instant case the claim encompasses treating cancer by administering to a human having cancer with cells expressing a cell surface antigen, an immunostimulatory nucleic acid and an IgG1 antibody which binds to a cell surface antigen of the cancer cell. Therefore, the claim encompasses antibodies for cell surface antigens that have not been identified (i.e. unknown antigens). The claims encompass molecules which have not been adequately described by the specification. Specifically, the claims encompass cell surface antigens which have not been adequately described in the specification as well as antibodies specific for the surface antigens. The specification indicates a number of cell surface antigens which are expressed on the surface of certain human cancer cells such as: CD20, CD40, CD22, CD19, etc. However, there is no disclosure indicating any common attributes or structural elements which are common

to all surface antigens on all cancer cells. Therefore, the claim encompasses antigens and antibodies which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim encompasses treating cancer by administering an immunostimulatory nucleic acid and an IgG1 antibody which binds to a cell surface antigen of a cancer cell. Therefore, the claim encompasses cell surface antigens that have not been identified (i.e. unknown antigens) and antibodies specific for these surface antigens. As mentioned in the written description rejection above, the claim encompasses antigens and antibodies which are not adequately described in the specification. Therefore, additional experimentation is required in order for one of skill in the art to be able to make and use the invention with a reasonable expectation of success. In order to make and use the claimed invention, a description of the surface antigens which would be representative of all surface antigens encompassed by the claim would have to be present. Regarding the description of a representative number of species, the written description guidelines note, "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999,

Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features other than the fact the all of the antigens are surface antigens are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of surface antigens encompassed by the claims.

Although the production of antibodies themselves does not require undue experimentation, the production of antibodies for unknown antigens does require an undue amount of additional experimentation considering the amount of work required to identify the unknown antigens. Therefore, it is concluded that an undue amount of additional experimentation is required for one of skill in the art to be able make and use the broadly claimed invention.

Response to Arguments

21. Applicant's arguments filed 7/11/03 have been fully considered but they are not persuasive.

Applicants contend that the specification discloses the common features of the antibodies encompassed by the claim: namely that each antibody is specific for a "surface antigen" and each antibody is an antibody of IgG1 isotype. Applicants contend that that one of skill in the art could practice the invention using a single antibody and a single immunostimulatory nucleic acid having these common features without undue experimentation.

In response, it is respectfully pointed out that the specification has not adequately described the surface antigens encompassed by the claims. Therefore, the specification has also not adequately described the antibodies specific for these surface antigens. Although the

applicants describe the antibodies as those specific for "surface antigens" and being an IgG1 isotype antibody, this is insufficient description because the specification has not adequately described the surface antigens encompassed by the claims for the reasons set forth above. Without an adequate description of the surface antigens encompassed by the claims, there is clearly not an adequate description of the IgG1 antibodies specific for these antigens. In order to practice the claimed invention, one of skill in the art would have to first identify a representative number of surface antigens encompassed by the claims; i.e., one would have to sufficiently identify the common attributes/structural features of the surface antigens encompassed by the claims such that all surface antigens encompassed by the claims could be identified based on those common attributes/structural features. A surface antigen expressed at a different level in a cancer cell compared to a normal cell is not an adequate description for all of the surface antigens encompassed by the claims. Therefore, additional experimentation is required in order to identify the surface antigens encompassed by the claims. Considering that the claims require the identification of the surface antigens encompassed by the claims and further require IgG1 isotype antibodies specific for these antigens, it is concluded that an undue amount of additional experimentation is required to practice the claimed invention.

Miscellaneous

The rejection of claims under 35 USC 102 (a) and (b) and the rejection of claims under 35 USC 103 have been withdrawn in view of the amendment and/or persuasive arguments.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 3, 4, 22 and 76 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
AU 1635

DAVE T. NGUYEN
PRIMARY EXAMINER